Kidney International, Vol. 28 (1985), pp. 541–549

Protective adaptation of low serum triiodothyronine in patients with chronic renal failure

VICTORIA S. LIM, MICHAEL J. FLANIGAN, DONALD C. ZAVALA, and RICHARD M. FREEMAN

Divisions of Nephrology and Hypertension and Pulmonary Diseases, Department of Internal Medicine, Veterans Administration Medical Center and University of Iowa College of Medicine, Iowa City, Iowa, USA

Protective adaptation of low serum triiodothyronine in patients with chronic renal failure. Low serum triiodothyronine (T_3) concentration is frequently found in patients with chronic renal failure (CRF). To test the hypothesis that this may serve to minimize protein catabolism in these patients, we measured nitrogen balance (Nb) in seven CRF and four control subjects in the basal state and when serum T_3 concentration was elevated by L-triiodothyronine (LT_3) and suppressed by sodium ipodate administration. In the basal state, both the controls and the CRF patients were in positive Nb, 0.02 ± 0.51 and 0.58 ± 0.34 g/day, respectively. During LT_3 administration, Nb decreased to −0.80 ± 0.39 g/day in the CRF patients ($P < 0.01$), but remained positive, 0.22 ± 0.67 g/day, in the controls. There was a significant negative correlation between serum T_3 concentration and Nb in the CRF patients ($r = -0.63$, $P < 0.005$), but not in the controls. Furthermore, urea nitrogen generation rate, calculated from urea kinetics, increased from a baseline of 4.6 ± 0.55 to 6.0 ± 0.50 mg/min during LT_3 administration in the CRF patients ($P < 0.01$). Sodium ipodate, which significantly lowered serum T_3 concentrations, had little effect on nitrogen metabolism in the controls and the CRF patients. These data support the concept that low serum T_3 concentrations may confer a protective effect on CRF patients regarding protein-nitrogen conservation and provide a rationale for not correcting such deficiency.

Adaptation protectrice d'une triiodothyronine sérique basse chez des malades atteints d'insuffisance rénale chronique. Une concentration faible de triiodothyronine sérique (T_3) est souvent trouvée chez des malades atteints d'insuffisance rénale chronique (CRF). Afin de vérifier l'hypothése que ce fait pourrait contribuer à minimiser le catabolisme protéique chez ces malades, nous avons mesuré la balance azotée (Nb) chez sept CRF, et chez quatre sujets contrôles à l'état basal, et lorsque la concentration sérique de T_3 était élevée par l'administration de L-triiodothyronine (LT_3), ou supprimée par celle d'ipodate de sodium. A l'état basal, les contrôles et les malades CRF avaient une Nb positive, 0,02 ± 0,51 et 0,58 ± 0,34 g/jour, respectivement. Au cours de l'administration de LT_3, Nb a diminué à −0,80 ± 0,39 g/jour, chez les malades CRF ($P < 0,01$), mais est restée positive, 0,22 ± 0,67 g/jour, chez les contrôles. Il existait une corrélation négative significative entre la concentration sérique de T_3 et Nb chez les malades CRF ($r = 0,63$, $P < 0,005$), mais non chez les contrôles. De plus, la vitesse de génération de l'azote uréique, calculée à partir de la cinétique de l'urée, a augmenté d'une valeur de base de 4,6 ± 0,55 à 6.0 ± 0,50 mg/min pendant l'administration de LT_3 chez les malades CRF ($P < 0,01$). L'ipodate de sodium, qui diminuait significativement les concentrations sériques de T_3, avait peu d'effets sur le métabolisme azoté chez les contrôles et les malades CRF. Ces données sont en faveur du concept que des concentrations sériques de T_3 basses pourraient conférer un effet protecteur chez les malades CRF en ce qui concerne la conservation protéique et azotée, et apportent un argument pour ne pas corriger ce déficit.

Received for publication December 26, 1984,
and in revised form March 5, 1985

A reduction in serum triiodothyronine (T_3) concentration is well documented in chronic renal failure (CRF) patients [1–4]. The significance of this finding, however, remains speculative. It has been hypothesized that low serum T_3 concentration in these patients has a biologic function, representing, perhaps, a metabolic adaptation for energy conservation [5]. In addition, T_3 administration has been advocated by some to increase the well-being of these patients. We suspect that low serum T_3 concentrations in these patients has an important function because previous work from our group in uremic rats indicated that T_3 deficiency is also present at the tissue level, specificially, the liver. Moreover, thyroid hormone-dependent enzyme activity and nuclear T_3 receptor-binding capacity are also reduced [6, 7]. In the current study, we attempted to test the validity of the above hypothesis and to resolve the controversial issue concerning T_3 administration by measuring nitrogen balance and oxygen consumption in CRF patients in the basal state and during periods when serum T_3 concentrations were altered by either L-triiodothyronine (LT_3) or sodium ipodate administration. The former increased and the latter suppressed serum T_3 concentrations further [8, 9]. The results showed an increased nitrogen excretion during LT_3 administration and support the concept that decreased T_3 production may, indeed, have a protective effect in minimizing protein nitrogen catabolism in patients with renal failure.

Methods

Subjects

The population of the current study consisted of seven CRF patients and four control subjects. There were four women and three men in the CRF group whose ages ranged from 20 to 59 years with the mean age being 42.8 ± 6.0 (SEM) years. The etiologies of their chronic renal failure were as follows: four, chronic glomerulonephritis; two, congenital urinary tract obstruction, and one, polycystic kidney disease. Their endogenous urea clearance rates ranged from 0 to 0.5 ml/min. Six patients were treated with hemodialysis and one (RB) with chronic ambulatory peritoneal dialysis (CAPD). The patients were selected on the basis of a low serum T_3 concentration (at

least one standard deviation below our mean). In 18 normal subjects, mean serum T_3 concentration ± 1 SD is 137 ± 26 ng/dl. Additional criteria for patient selection included: *1)* normal serum TSH concentration (<10 μU/ml), *2)* absence of previous history of thyroid disease[1], *3)* clinically stable, and *4)* absence of angina pectoris and congestive heart failure. Their medications included multivitamins, phosphate binders (alucaps and alternagel) and dihydrotachysterol. As mentioned in the footnote, JS was taking L-thyroxine (LT_4) and APL was taking 40 mg/day of propanolol for mild hypertension. The normal control subjects consisted of three women and one man; their ages ranged from 25 to 49 and their mean age was 33.0 ± 5.4 years. The body mass indices (Wt/Ht^2) were in the 49 ± 17 and 43 ± 13 percentile, respectively, for the CRF patients and the controls as compared to age and sex-matched normal subjects of the NHANES-1 Survey [10].

Experimental design

Each participant, control subject as well as CRF patient, was studied on three separate occasions: in the basal state, during L-T_3 (Cytome®) administration, and during sodium ipodate (Oragrafin®) administration. Each study period lasted 9 days and the sequences of the three periods were assigned randomly. In all seven CRF patients and in three control subjects, LT_3 was given at a total daily dose of 50 μg orally in four equally divided doses, in one control subject (JH), because of his higher body weight, LT_3 was given at a total daily dose of 75 μg orally in three equally divided doses. Corrected for body wt, the dosages of LT_3 were 0.78 ± 0.05 and 0.84 ± 0.08 μg/kg, respectively, in the CRF patients and the controls; the values were not different statistically. The dose of sodium ipodate was 1 g per day orally. Both LT_3 and sodium ipodate were given for a period of 2 weeks, 1 week before the study and 1 week during the study. One CRF patient (RB) did not complete the sodium ipodate study because of the development of pruritic macular rash. Measurements during each study period included: *1)* nitrogen balance, *2)* serum thyroid hormone profile, *3)* TRH test, *4)* basal oxygen consumption, and *5)* urea nitrogen generation rate (G_u) in the six hemodialysis patients. The last parameter served to assess protein catabolic rate independent of nitrogen balance measurement.

Nitrogen balance study

Figure 1 illustrates the protocol followed by the CRF patients with regard to diet and the timing of urine and fecal collection and dialyses. Each patient was admitted to the Clinical Research Center and was placed on a constant diet starting Sunday morning and continued for at least 9 days until the following Monday noon. The diet was specifically adjusted for each subject based on his/her usual intake and dietary habits which were derived from interviews with the nutritionist as well as a diary of food intake. The menu plan was discussed extensively with each subject and once agreed upon was held constant throughout the three study periods. Sufficient amount of food was prepared in a whole batch for the entire study. Since neither the protein nor the energy allotment was different from their routine intake at home, a long period of equilibration was not needed. A 7-day urine collection was started Monday morning and ended the following Monday, the specimens were pooled and kept refrigerated. A 6-day stool collection was marked by carmine red ingestion on Monday and Saturday and was kept refrigerated as well. Hemodialysis was performed with the AK10 Gambro Delivery System and the Gambro parallel flow dialyzer 11.5 (Gambro, Barrington, Illinois, USA) four times during each study. Dialysate obtained on the first dialysis was discarded and that of the three subsequent ones were saved. Dialysate outflow from the entire dialysis was collected *in toto* into a 120-liter tared container. At the end of the dialysis, the dialysate was mixed thoroughly and triplicate 50 ml dialysate samples were taken for measurements of nitrogen and urea nitrogen; the container, together with the dialysate, were then weighed for dialysate volume determination assuming a specific gravity of 1.000. Additionally, the change in body urea nitrogen pool (g/day) was calculated with the following formula: $(SUN_f - SUN_i)\ BW_i \times 0.6 + (BW_f - BW_i)\ SUN_f$ where SUN = serum urea nitrogen (mg/ml), BW = body weight (kg), i and f represent the initial and the final points, respectively, of each balance period. This formula assumes that the volume of distribution of urea is total body water and that short-term changes in body wt represent changes in body water. Positive values denote urea N accumulation and negative ones, urea N loss. There were altogether three sets of data available for each study period, defined as the end of one dialysis session to the end of the subsequent dialysis session. Food not consumed or vomited was recorded and portions of the diet analyzed separately for nitrogen content. All patients, except JS, were stable and ingested all meals and snacks.

In the one patient (RB) who was treated with CAPD, body weight and SUN were determined every morning after draining off the overnight dialysate and before instilling the first volume of fresh dialysate solution. Every bag of dialysate was weighed after drainage for determination of dialysate volume and duplicate samples were taken for measurements of nitrogen and urea nitrogen concentration.

In the controls, similar procedures were followed with regard

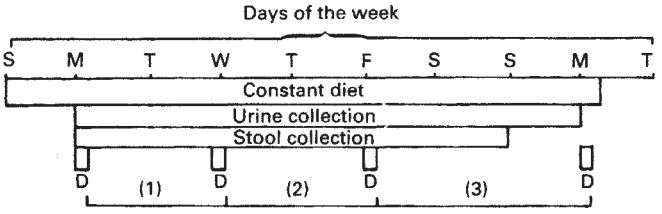

Fig. 1. *Schematic representation of the protocols used by the CRF patients.* Shown here are the duration of the constant diet and the schedules of dialysis (D) and urine and fecal collection. First dialysate was discarded and the subsequent three were used for estimation of nitrogen balance.

[1]JS was taking 0.2 mg of L-thyroxine [LT_4, Synthroid®] each day for 6 months, approximately the same duration as her chronic renal failure and dialysis. We were not certain whether she was truly hypothyroid or whether she was simply given thyroid hormone replacement because of low circulating thyroid hormone concentration consequent to uremia. It is interesting to note that despite a high normal serum total T_4 concentration of 9.2 μg/dl, her serum T_3 concentration was markedly reduced at 64 ng/dl, and her serum TSH concentration was normal. Thus, it was decided to study her while she was taking the same amount of (LT_4) in all three periods.

to menu planning. Like the CRF patients, stool collections were pooled for a 6-day period. Urine collections were done separately each 24 hr for 7 consecutive days. The control subjects were allowed to take their prescribed meals and collect the urine and fecal samples at home; the samples were kept refrigerated. As all the control subjects were hospital workers; the samples were brought in daily. Each participant was encouraged to drink abundant amounts of fluid so as to increase the accuracy of urine collection. There were seven sets of data for each study period.

Physical activities varied considerably from person to person. No attempts were made to equalize activities among the experimental subjects, but each was advised to maintain the same amount of phsyical activities in all three study periods. The chronic renal failure patients, although freely ambulatory, were generally quite sedentary. The control subjects continued to perform their duties in the hospital and one subject (JA) who jogged 3 miles each day continued to do so.

Urea nitrogen generation rate (G_u) and urea space (Vurea)

In the six CRF patients who were treated with maintenance hemodialysis, G_u was calculated by the methods of Sargent and Gotch [11, 12]. During each dialysis, urea clearance of the artificial kidney was determined at 1/2, 1 and 2 hr by measuring the dialysate out flow rates and the urea N concentrations of the dialysate out flow and the arterial blood samples. Body wt and SUN were determined pre- and post-dialysis. The time intervals between two consecutive dialyses and the duration of each dialysis were accurately recorded. Residual renal urea N clearance was estimated by a 7-day urine collection and daily urinary urea N excretion was assumed to be 1/7 of the total output; SUN was also measured on the days between dialyses. A computer program was written for calculating urea kinetics utilizing the above data.

Serum thyroid hormone measurements and TRH test

Serum total T_3 concentration (TT_3) was measured 2 hr after each dose of LT_3 and immediately before the next dose for 2 days during LT_3 administration; the mean of the former was designated as the peak and the latter, the trough value. Total T_4 and free T_4 concentration were measured on the same blood samples as TT_3. During the basal and sodium ipodate periods, blood samples were taken at the same time as in the LT_3 period. The values from each study period were averaged and the mean values used in the statistical analysis. For the TRH test, thyrotropin-releasing hromone, 500 μg, was given as a single bolus intravenous injection and blood samples were taken 30 and 15 min before and 15, 30, 45, 60, 90, 120, and 180 min after the injection for measurement of thyroid stimulating hormone (TSH).

Basal oxygen consumption (BOC)

BOC was measured 10 to 12 hr in the post absorptive state after the subjects had rested for a minimum of half an hour in a semi-reclining chair. The room was quiet; the temperature and lighting were comfortable. Participants were given sufficient time to become familiar with the equipment and the procedures.

Oxygen consumption was determined with the MEDICAL GRAPHIC EXCERCISE SYSTEM 2000, which utilized a waveform breath-by-breath analyzer (Medical Graphics Corp., St. Paul, Minnesota, USA). Continuous expired gas samples were obtained 100 times/sec and P_{O_2} measured by a zirconium high-temperature fuel cell (750°C) O_2 analyzer (Model S-3A, Applied Electrochemistry, Inc., Sunnyvale, California, USA). The analog outputs of the O_2 analyzer were connected to a Tektronix 4052 computer (Tektronix, Inc., Beaverton, Oregon, USA) via a multichannel analog-to-digital converter (Medical Graphics Data Interface 704). During the period of testing, the expired air was collected for quality control into a 120 liter Douglas bag and the percentage of O_2 measured separately by the same analyzer [13]. These results were well correlated with the breath-by-breath measurements.

Laboratory procedures

1) Serum TT_4, free T_4 and TT_3 concentrations were measured by radioimmunoassays using commercially available kits (Clinical Assays, Cambridge, Masschusetts, USA). Serum TSH concentration was also measured by radioimmunoassay using antibody prepared by Calbiochem-Behring (San Deigo, California, USA) and iodinated tracer prepared by Radioassay Systems Laboratories (Carlson, California, USA).

2) Total nitrogen (N) concentration in the dialysate, urine, feces, and food was measured by the modified Kjeldahl method [14].

3) Urea N concentration was measured with the Technicon Autoanalyzer using diacetyl monoxime.

The protocols were approved by the Clinic Research Center Committee and the Committee on Research Involving Human Subjects of the Veterans Administration Medical Center and the University of Iowa Hopsitals and Clinics.

Statistical analysis

The calculation of urea nitrogen generation rate and urea space as well as all statistical analyses were done on the CLINFO SYSTEM of the Clinical Research Center at the University of Iowa. All values are reported as means ± SEM. Student's *t* test, paired *t* test, and analysis of variance were used to evaluate the significance of the differences between the two experimental groups and between different test periods within the same group.

Results

Serum thyroid hormone profile and thyroid-pituitary feedback

Table 1 summarizes the results of the thyroid hormone profile in the basal state and the changes following LT_3 and sodium ipodate administration. In the basal state, the most important difference between the CRF patients and the control subjects was a reduction in the serum concentration of total T_3, 79 vs. 111 ng/dl, $P < 0.005$. Mean serum total and free T_4 concentration were not different from one another. It should, however, be clarified that one of the CRF patients, JS, was taking 0.2 mg/day of LT_4 during the study, which very likely elevated the mean serum T_4 concentration in the CRF group. When her values were eliminated from the calculations, mean serum total and free T_4 concentration in the remaining six CRF patients were, respectively, 7.13 ± 0.34 μg/dl and 1.17 ± 0.22 ng/dl. These values, although lower than those listed in Table 1, are still statistically not different from those of the controls. Basal

Table 1. Serum thyroid hormone profile in patients with chronic renal failure and normal subjects in the basal state and during L-triiodothyronine (LT_3) and sodium ipodate administration

	TT_4 μg/dl	FT_4 ng/dl	TT_3 ng/dl		TSH_b μU/ml	TSH_p μU/ml
CRF patients (7)						
Basal	7.42 ± 0.40	1.14 ± 0.15	79 ± 5		5.2 ± 1.6	17.2 ± 5.8
LT_3	5.51 ± 0.83*	0.83 ± 0.10*	172 ± 16‡	134 ± 15‡	1.5 ± 0.5	2.9 ± 0.7*
Ipodate	8.89 ± 0.73*	1.31 ± 0.17	66 ± 9*		9.1 ± 2.4*	23.0 ± 6.0*
$P^{\S}$	< 0.01	NS	< 0.001		< 0.05	< 0.05
Normal subjects (4)						
Basal	7.40 ± 0.36	1.56 ± 0.15	111 ± 6		2.2 ± 0.3	12.1 ± 1.9
LT_3	5.28 ± 0.25*	1.00 ± 0.09‡	214 ± 12‡	180 ± 13‡	1.0 ± 0.3	1.5 ± 0.4*
Ipodate	9.60 ± 1.04	1.89 ± 0.22	74 ± 8		2.4 ± 0.5	18.3 ± 2.4‡
$P^{\S}$	< 0.005	<0.05	<0.001		NS	< 0.001

All values are presented as means ± SEM. TT_4, FT_4, and TT_3 refer to total thyroxine, free thyroxine, and total triiodothyronine, respectively. Parentheses indicate the number of subjects. During LT_3 treatment period, TT_3 levels are reported as peaks and troughs. TSH_b and TSH_p represent basal values and peak responses following 500 μg of TRH. * and ‡indicate P values of < 0.05 and < 0.01, comparing LT_3 and sodium ipodate treatment data to their respective basal values by paired t test. §P values derived from analysis of variance.

Table 2. Nitrogen balance data in patients with chronic renal failure and normal subjects in the basal state and during L-triiodothyronine and sodium ipodate administration

	Nd	Nu	Nf	ΔUN pool	Nin	Nb	G_u	Vurea	Intake/day Protein	Intake/day Energy
	g/24 hr						mg/min	liter	g/kg	Kcal/kg
CRF patients (7)										
B	7.43 ± 0.55	0.22 ± 0.12	0.93 ± 0.05	0.05 ± 0.19	9.21 ± 0.83	0.58 ± 0.34	4.62 ± 0.55	35.4 ± 3.0	0.87 ± 0.06	29.5 ± 1.5
T_3	8.60 ± 0.43*	0.26 ± 0.15	0.99 ± 0.10	0.12 ± 0.14	9.17 ± 0.81	−0.80 ± 0.39‡	6.00 ± 0.50‡	41.1 ± 4.4	0.88 ± 0.06	29.7 ± 1.8
Ip	6.60 ± 0.32	0.27 ± 0.13	0.84 ± 0.11	0.11 ± 0.15	8.70 ± 0.78	0.87 ± 0.37	4.72 ± 0.60	35.0 ± 2.3	0.84 ± 0.07	28.8 ± 2.6
$P^{\S}$	< 0.05	NS	NS	NS	NS	< 0.01	NS	NS	NS	NS
Normal subjects (4)										
B		13.18 ± 0.70	1.52 ± 0.07		14.72 ± 1.12	0.02 ± 0.51			1.57 ± 0.18	39.9 ± 1.3
T_3		12.92 ± 0.53	1.65 ± 0.08		14.79 ± 1.12	0.22 ± 0.67			1.57 ± 0.18	40.3 ± 1.4
Ip		12.88 ± 0.73	1.69 ± 0.30		14.61 ± 0.90	0.05 ± 0.60			1.58 ± 0.18	40.4 ± 1.5
$P^{\S}$		NS	NS		NS	NS			NS	NS

All values are presented as means ± SEM. B, T_3 and Ip represent basal state, LT_3, and sodium ipodate administration periods. Nd, Nu, Nf, and Nin = nitrogen content of dialysate, urine, feces, and food and Nb = nitrogen balance. ΔUN pool = changes in body urea pool (see **Methods**). G_u and Vurea represent urea N generation rate and urea space, calculated by the methods of Sargent and Gotch [10, 11]. Parentheses indicate the number of subjects. * and ‡indicate P values of < 0.05 and < 0.01, respectively, comparing LT_3 and sodium ipodate administration results with the baseline data within the same group by paired t test. §P values derived from analysis of variance.

serum TSH concentration and TSH peak responses to TRH appeared to be slightly higher in the CRF patients, but the differences were not statistically significant. LT_3 administration raised serum T_3 concentration in every subject tested. The peak fractional increments, 118% in the CRF patients and 93% in the controls, were not different. Both serum total and free T_4 concentration were significantly reduced during LT_3 administration in the control and the uremic subjects, this was accompanied by equally significant suppression of serum basal TSH concentration and peak TSH response to TRH. Sodium ipodate significantly reduced serum T_3 concentration in both groups; fractional decrements were 16% in the CRF patients and 33% in the normal subjects. The lesser magnitude of reduction in the CRF patients was, perhaps, related to their lower basal values. Serum total and free T_4 concentration increased and TSH response to TRH became exaggerated.

Nitrogen balance

Table 2 compares the nitrogen balance data of CRF patients and normal subjects in the basal state and the changes that occurred during LT_3 and sodium ipodate administration. In CRF patients, nitrogen intake (Nin) was lower than that of the controls, 9.21 vs. 14.72 g/day, $P < 0.005$. In the basal state, total nitrogen output (Nd + NU + Nf), 8.63 g/day in the CRF patients, was also proportionately lower than that of the controls, being 14.70 g/day, $P < 0.001$. Thus, like the controls, uremic patients maintained a slightly positive nitrogen balance. While approximately 89% of the nitrogenous waste was ex-

Table 3. Nitrogen balance data in each individual subject in the basal state and during L-triiodothyronine administration

		Nd	Nu	Nf	ΔUN pool	Nin	Nb	G_u
		g/24 hr						*mg/min*
CRF patients								
IJ	B	7.06	0.01	0.73	0.41	8.64	0.43	5.30
	LT_3	8.55	0.01	1.23	0.12	8.83	−1.08	7.05
JS	B	6.59	0.42	1.01	−0.72	7.33	0.03	4.02
	LT_3	9.23	0.37	0.68	−0.59	6.95	−2.74	5.90
BM	B	8.39	0	0.93	0.29	10.61	1.00	5.71
	LT_3	8.82	0.06	1.18	0.43	10.43	−0.07	6.62
MJ	B	5.53	0	0.84	−0.05	6.15	−0.16	2.65
	LT_3	6.50	0	0.57	−0.01	6.46	−0.60	3.70
JG	B	6.84	0.85	1.09	0.82	11.79	2.19	3.84
	LT_3	8.85	1.05	1.22	0.56	11.93	0.25	5.90
RB	B	10.09	0	0.89	−0.29	11.71	1.03	—
	LT_3	10.21	0	1.06	0.21	11.42	−0.06	—
AL	B	7.50	0.29	1.00	−0.11	8.26	−0.42	6.20
	LT_3	8.05	0.36	0.98	0.12	8.18	−1.33	6.82
Normal subjects								
JH	B		14.74	1.43		17.13	0.97	
	LT_3		13.92	1.60		17.24	1.72	
PS	B		13.62	1.41		15.17	0.14	
	LT_3		13.61	1.45		15.48	0.42	
JA	B		11.39	1.73		11.72	−1.40	
	LT_3		11.59	1.81		11.87	−1.53	
ER	B		12.97	1.51		14.87	0.39	
	LT_3		12.54	1.76		14.56	0.26	

See footnotes of Tables 1 and 2. For the CRF patients, ND and ΔUN pool were determined three times per study period and for the controls, Nu was determined daily for the 7 days of the study period; the mean values are listed above. B and T_3 represent basal and LT_3 periods, respectively.

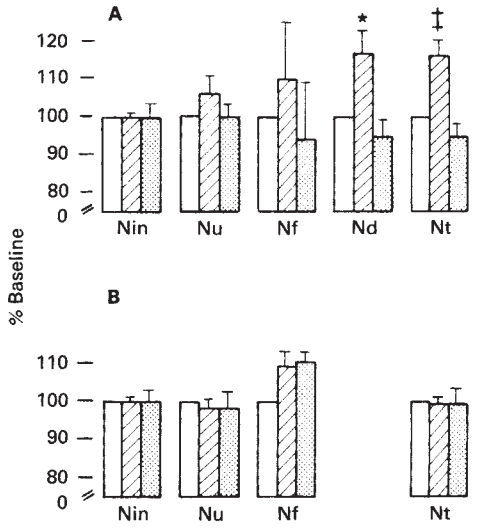

Fig. 2. *Comparison of nitrogen balance data between the seven CRF patients* (Panel **A**) *and the four normal subjects* (Panel **B**). Changes in nitrogen content of food (Nin), urine (Nu), feces (Nf), and dialysate (Nd) as well as total nitrogen output (Nt = sum of Nu, Nf, Nd, and Δ urea N pool) during the LT_3 (▨) and sodium ipodate (▩) administration periods are presented as percentage of baseline (□), taken as 100%. All values are presented as means ± SEM. Only in the CRF patients did Nd and Nt became significantly increased during LT_3 administration, * $P < 0.05$ and ‡$P < 0.01$ by paired t test.

creted in the urine in the normal subjects, about 85% was removed by the dialysate in the uremic patients. Fecal nitrogen constituted about 10 to 12% of the total nitrogen output in both groups of subjects although the absolute amount was lower in the CRF patients. During LT_3 administration, nitrogen balance was well maintained in the normal subjects. By contrast, nitrogen output increased markedly in the CRF patients, from 8.63 in the basal state to 9.97 g/day. Since nitrogen intake was almost identical, nitrogen balance became negative, −0.80 g/day. This increase in nitrogen catabolism is accounted for by nitrogen removal via dialysis because neither the nitrogen excretion in the urine and the feces nor the urea nitrogen pool were significantly altered. Upon sodium ipodate administration, nitrogen balance remained stable in the control subjects. In the uremic patients, total nitrogen output was 7.82 g/day, a value lower than that of the basal period. However, since nitrogen intake was also lower during this period, the mean nitrogen balance of 0.87 g/day was not different from the basal period.

Also listed in Table 2 are the protein and energy intake as calculated from the dietary records; both were significantly lower in CRF patients, $P < 0.005$. Within each group, both protein and energy intake, however, were constant for all three periods.

Table 3 records the individual nitrogen balance data of all subjects in the basal period and during LT_3 administration. In the basal period, five CRF patients were in positive nitrogen balance and in three of them, (BM, JG, and RB), nitrogen retention was quite substantial, being 1.00, 2.19, and 1.03 g/day, respectively. During LT_3 treatment, four of these patients went into negative nitrogen balance ranging from −0.07 to −2.74 g/day. JG, who originally had a positive balance of 2.19 g/day, decreased to 0.25 g/day. MJ and AL were originally in slightly negative balance and became more severely negative. While changes in urinary (Nu) and fecal (Nf) nitrogen excretion as well as urea nitrogen pool (UN) were random and insignificant; increases in urea nitrogen removal by dialysis (Nd) were consistent in every CRF patient. By contrast, nitrogen balance in the four control subjects was not altered by LT_3 administration. In three controls, positive nitrogen balance was observed during both the basal and the LT_3 periods, and in one (JA), comparable negative balances were noted during both periods.

Figure 2 depicts and compares the changes in nitrogen intake and output in the CRF patients and the normal subjects. Values obtained in the basal state were taken as 100% and those obtained during experimental periods were expressed as percent of baseline. Only the mean dialysate nitrogen and the mean total nitrogen output of the CRF patients increased significantly to 117 ± 6% and 116 ± 4%, respectively, during LT_3 administration. In the controls, nitrogen intake and output remained stable throughout the three periods.

Urea nitrogen generation rate (G_u) and urea space (Vurea)

Urea nitrogen generation rate and urea space were measured only in the hemodialysis patients and the results are listed in Table 2. Mean G_u for the group was 4.62 mg/min in the basal state and increased to 6.00 mg/min during LT_3 administration, $P < 0.05$. During sodium ipodate treatment, G_u was 4.72 mg/min.

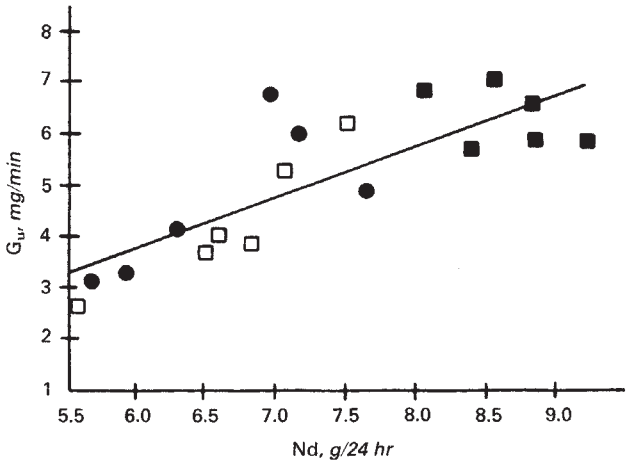

Fig. 3. *Relationship between urea nitrogen generation rate (G_u) and nitrogen removal by dialysis (Nd) in six hemodialyzed CRF patients in the basal state (□), during LT_3 (■), and sodium ipodate (●) administration, showing a significant positive correlation between these two parameters. ($N = 18$, $r = 0.81$, and $P < 0.001$, $G_u = 1.01 \times Nd - 2.23$).*

Table 4. Basal oxygen consumption in patients with chronic renal failure and normal subjects in the basal state and during L-triiodothyronine and sodium ipodate administration

	BMI kg/m^2	VO_2 ml/min	VO_2/BW ml/kg/min	VO_2/BMI ml/min/kg/m^2
CRF patients (7)				
Basal	26.6 ± 2.7	190 ± 11	2.94 ± 0.16	7.46 ± 0.72
LT_3		186 ± 10	2.90 ± 0.20	7.40 ± 0.81
Ipodate		169 ± 13	2.69 ± 0.22	6.45 ± 0.70
P§		NS	NS	NS
Normal subjects (4)				
Basal	22.5 ± 1.8	166 ± 30	2.65 ± 0.12	7.26 ± 0.84
LT_3		191 ± 31*	3.08 ± 0.09*	8.40 ± 0.81*
Ipodate		159 ± 26	2.56 ± 0.08	7.00 ± 0.73
P§		NS	< 0.05	NS

See footnote for Table 1. BMI = body mass index, BW = body weight. All values are presented as means ± SEM. Parentheses indicate the number of subjects. * = $P < 0.005$ comparing LT_3 to basal value within each group by paired t test. §P values derived from analysis of variance.

Vurea, however, was not significantly altered by either LT_3 or sodium ipodate administration. As shown in Table 3, G_u increased in every CRF patient. Figure 3 shows that G_u correlated well with nitrogen removal by dialysis (Nd) in the six hemodialyzed CRF patients ($N = 18$, $r = 0.81$ and $P < 0.001$. $G_u = 1.01 \times Nd - 2.23$).

Basal oxygen consumption

The data on BOC are summarized in Table 4. Body mass index appeared to be higher in the patient group, but the difference was not statistically significant. Oxygen consumption in the basal state was not different between the two groups. The response to LT_3 administration, however, was different, the normal subjects showed an increase in oxygen consumption, either in absolute values or corrected for body weight or body mass index. By contrast, the uremic patients showed no increment. Sodium ipodate appeared to decrease oxygen consumption in both groups of subjects, but this did not achieve statistical signfiicance when compared to basal values.

Discussion

This study demonstrates that patients with CRF undergoing dialysis are able to maintain a positive nitrogen balance despite a lower protein and energy intake than normal subjects. During LT_3 administration, CRF patients developed a less positive or more negative nitrogen balance whereas nitrogen balance in normal subjects was unchanged. This differential response to LT_3 administration between the normal controls and the CRF patients suggests the presence of abnormalities in the intermediary protein metabolism of CRF patients, which is characterized by increased sensitivity to the catabolic effects of thyroid hormone.

It could be argued that the amount of LT_3 administered in the present study, 50 μg/day, is higher than the physiologic production rate, which is generally estimated to be about 35 to 40 μg/day [15, 16]. Moreover, the mean trough serum T_3 concentration of 134 ng/dl in the CRF patients during LT_3 treatment was not only higher than their own basal value of 79 ng/dl, but was also higher than the mean basal value of 111 ng/dl in the controls. Therefore, one would not be surprised to find some degree of increased catabolism. This argument, however, should be viewed in light of the observation that equivalent doses of LT_3 in the controls did not produce any catabolic effect despite achieving an even higher level of mean trough serum LT_3 concentration of 180 ng/dl. Treatment with sodium ipodate resulted in an easily discernible reduction in serum T_3 concentration, a significant rise in serum total and free T_4 concentration, and an exaggerated TSH response to TRH. These findings are in agreement with those reported by Burgi et al and Kleiman and his colleagues [8, 9]. In contrast to the changes found in the serum, sodium ipodate appeared to have little effect on nitrogen metabolism. In the CRF patients, nitrogen balance became more positive in three and unchanged in the other three; the mean value, however, was not different from that obtained in the basal state.

While nitrogen balance in the normal subjects appeared not to be affected by LT_3 administration, that of CRF patients was quite sensitive to it. This difference is illustrated in Figure 4 in which nitrogen balance is plotted against serum TT_3 concentration, which ranged from 43 to 243 ng/dl. In CRF patients (Panel A), there is a significant negative correlation between these two parameters, $r = -0.629$ and $P < 0.005$. Nitrogen balance decreased as serum T_3 concentrations increased. Nitrogen balance became negative when serum TT_3 concentration exceeded 125 ng/dl (calculated from the linear regression line, Nb $= -0.013 \times$ serum $TT_3 + 1.61$). In the controls (Panel B), there was no correlation between nitrogen balance and serum T_3 concentration. The three negative balances ranging from −1 to −1.5 g/day were from the same subject who possibly underestimated her intake.

The lack of catabolic effect in the controls was not due to failure of the control subjects to take the prescribed amount of LT_3 because the serum T_3 concentration increased and the TSH response to TRH was suppressed in each control subject.

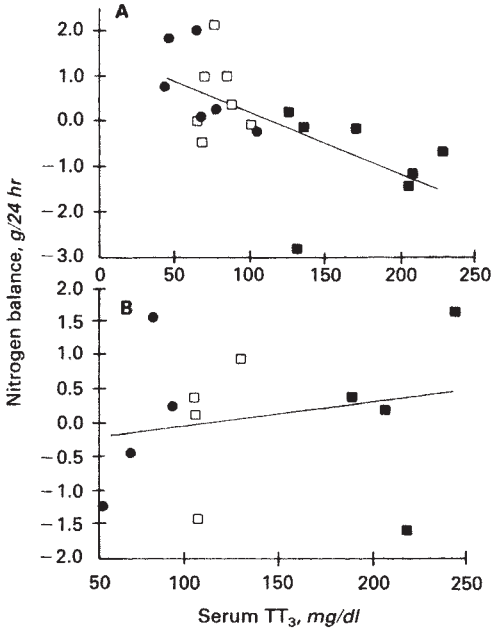

Fig. 4. *Effect of changing serum TT_3 concentrations on nitrogen balance (Nb) in CRF patients and normal subjects.* In CRF patients (Panel **A**), low serum TT_3 concentrations obtained in the basal state (□) and during sodium ipodate treatment (●), were associated with positive or mildly negative Nb whereas high serum TT_3 concentration, achieved with LT_3 (■) administration, resulted in negative Nb ($N = 20$, $r = -0.629$, and $P < 0.005$, $Nb = -0.013 \times$ serum $TT_3 + 1.61$). Nb became negative when serum TT_3 concentration exceeded 125 ng/dl, below which Nb was positive. In the normal subjects (Panel **B**), there was no correlation between serum TT_3 concentration and Nb ($N = 12$, $r = 0.20$, and $P = 0.53$).

Virtually all the increment in nitrogen output in the CRF patients during LT_3 administration was accounted for by removal in the dialysate, as urinary and fecal nitrogen excretion were little changed. The changes in urea nitrogen pool from the beginning to the end of each period were generally small and were not different between the basal period and during LT_3 administration. This is explained partially by our experimental design in which both the beginning and the end of each balance period occurred at the end of a dialysis (Fig. 1), a time when both the SUN and the body weight were closest to normal.

Urea nitrogen generation rate provided an independent assessment of protein catabolic rate and in the CRF patients it increased from a basal value of 4.6 mg/min to 6.0 mg/min during LT_3 administration. This finding correlated very well with data obtained from the nitrogen balance technique using the Kjeldahl procedure.

Negative nitrogen balance in our patients could result from either a decrease in protein synthesis or an increase in protein degradation. Our data do not permit us to differentiate between these two possibilities. However, we speculate that increased muscle proteolysis may be a key factor because muscle contains the largest fraction of body protein store and increased muscle catabolism is a feature found in both hyperthyroidism and uremia.

It is well known that thyrotoxicosis is associated with increased urinary creatine excretion and negative nitrogen balance [17]. Furthermore, it has been demonstrated that urinary creatine excretion increases by tenfold in obese human subjects when LT_3 is administered during fasting compared to that observed during fasting without LT_3 administration [18]. Burman et al recently reported that LT_3 administration to obese human subjects resulted in increased urinary excretion of 3-methylhistidine, [19], a sensitive marker for muscle protein degradation [20].

Uremia and/or dialysis may also affect protein metabolism. In experimental models, various groups of investigators, including Mitch and Clark, Holliday, Garber, and Li and Wassner [21–25], have demonstrated that uremic rats are more prone to muscle proteolysis. In vitro preparations of different skeletal muscle showed an increased release of α-amino nitrogen, amino acids, as well as 3-methylhistidine, by the uremic rats as compared to their sham-operated controls during fasting. In humans, Ganda and colleagues showed that, following hemodialysis, whole blood and plasma concentrations of the branched chain amino acids, leucine and isoleucine, remained unchanged while that of glutamate increased. Since substantial quantities of these amino acids are removed by dialysis, constant or increasing concentrations were interpreted as evidence suggestive of enhanced release from muscle [26]. Thus, the prevailing evidence suggests that, in uremia, the balance between anabolism and catabolism is shifted towards net protein catabolism. In addition to vulnerability to fasting, we have demonstrated in this report an enhanced sensitivity to the catabolic effects of thyroid hormone, specifically, LT_3.

It is not clear whether this enhanced sensitivity to the catabolic effects of thyroid hormone observed in the CRF patients is due to uremia per se or, perhaps, related to their inadequate protein and caloric intake. Borah et al reported that dialysis patients required about 1.4 g/kg body wt of protein intake per day to avoid negative nitrogen balance [27]. It should be emphasized that the intake of our patients was determined on the basis of their usual dietary habits and no effort was made to resort to either protein or caloric supplementation. These intakes are not unique to our patient population and are fairly accurate reflections of the dietary pattern of most dialysis patients. A caloric intake of at least 35 Kcal/kg is usually recommended for CRF patients, especially when the protein intake is restricted, to achieve some protein-sparing effects [28]. The lower caloric intake of our patients, 30 Kcal/kg, may partly be responsible for the demonstrated hypersensitivity to thyroid hormone.

The pituitary-thyroid axis appeared to be entirely normal in CRF patients, as their responses to LT_3 and sodium ipodate administration were qualitatively and quantitatively similar to the controls. These findings corroborate very well with our studies in the rats showing that T_3 content in the pituitary of the uremic rats is normal. In other words, there is no evidence of hypothyroidism at the pituitary level. In striking contrast, T_3 content in the peripheral tissue, as represented by the liver, is reduced [6, 7]. Although we have no data on tissue T_3 content in the humans, extrapolation of animal model data would support the concept that peripheral tissue is "hypothyroid" in the sense that T_3 content of the liver or the muscle, if measured, would probably be reduced. In the uremic rat model, liver T_3 content is invariably reduced before a reduction in serum T_3 is noted. This functionally hypothyroid state in the peripheral tissue serves to defend against protein wasting in a precarious

situation in which the protein-caloric intake is limited and catabolism may be exaggerated. Thus, in CRF patients having low serum T_3 concentration, misguided attempts to "replete" thyroid hormone stores only serve to worsen the situation because their greater sensitivity to the protein catabolic effects of thyroid hormone causes them to go into negative or less positive nitrogen balance. Gardner et al reported similar findings in humans undergoing starvation. In their studies, normal subjects underwent fasting twice; once without any medication and a second time while receiving 40 μg/day of LT_3. Urinary urea nitrogen excretion increased significantly during period of LT_3 administration [29]. Their data and our current results thus constitute evidence supporting the concept that decreased T_3 production during illness may represent a common metabolic pathway of biologic adaptation for protein-nitrogen conservation and provide a rationale for not correcting such deficiency.

Basal oxygen consumption was not different between the normal and the uremic patients. The response to LT_3 administration, however, was different; while oxygen consumption increased in the normal subjects, it remained unchanged in the uremic patients. This resistance to thyroid hormone with regard to oxygen consumption was unexpected, especially in view of the sensitivity of protein catabolism to the same hormone. In the rat, Wimpfheimer and his co-workers found that starvation resulted in a lower resting oxygen consumption that increased very sluggishly during thyroid hormone treatment [30].

On the one hand, our patients showed enhanced sensitivity to thyroid hormone with regard to protein catabolism; on the other hand, their response to LT_3 in terms of oxygen consumption was blunted. This dichotomy of response to the same hormone, while puzzling, is not unexplainable. Enhanced sensitivity with regard to protein catabolism may be related to a number of potential causes, including insulin resistance, hyperglucagonemia, inadequate nutritional intake, and others. Failure of LT_3 to increase oxygen uptake in the uremic patients may be related to anemia or uremia per se.

Acknowledgments

The authors thank Dr. G. DiBona for critical review of this manuscript, Dr. B. Sherman for encouragement and discussions, and to Dr. S. Fomon for technical advice on nitrogen balance. We thank the Clinical Research Center and Hemodialysis Unit staff for patient care, P. Weber for technical assistance, and D. Hill for typing the manuscript.

This work was supported by Veterans Administration Merit Review Award (VSL) and by Grant RR59 from the General Clinical Research Center Program, Division of Research Resources, National Institutes of Health.

Reprint requests to Dr. V. S. Lim, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242 USA

References

1. Lim VS, Fang VS, Katz AL, Refetoff S: Thyroid dysfunction in chronic renal failure: a study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. *J Clin Invest* 60:522–534, 1977
2. Silverberg DS, Ulan RA, Fawcett DM, Dorsetor JB, Grace M, Beltcher K: Effects of chronic hemodialysis on thyroid function in chronic renal failure. *Can Med Assoc J* 109:282–286, 1973
3. Ramirez G, O'Neil W, Jubiz W Jr, Bloomer HA: Thyroid dysfunction in uremia. *Ann Intern Med* 84:672–676, 1976
4. Spector DA, Davis PJ, Helderman JH, Bell B, Utiger RD: Thyroid function and metabolic state in chronic renal failure. *Ann Intern Med* 85:724–730, 1976
5. Schimmel M, Utiger RD: Thyroidal and peripheral production of thyroid hromones. *Ann Intern Med* 87:760–768, 1977
6. Lim VS, Henriquez H, Seo H, Refetoff S, Martino E: Thyroid function in a uremic rat model: evidence suggesting tissue hypothyroidism. *J Clin Invest* 66:946–954, 1980
7. Lim VS, Passo Y, Murata Y, Ferrari E, Nakamura H, Refetoff S: Reduced triiodothyronine content in liver but not pituitary of the uremic rat model: Demonstration of changes compatible with thyroid hormone deficiency in liver only. *Endocrinology* 114:280–286, 1984
8. Burgi H, Wimpfheimer A, Burger A, Zaunbauer W, Rosler H, Lemarchand-Beraud T: Changes of circulating thyroxine, triiodothyronine and reverse triiodothyronine after radiographic contrast agents. *J Clin Endocrinol Metab* 43:1203–1210, 1976
9. Kleinmann RE, Vagenakis AG, Braverman LE: The effect of iopanic acid on the regulation of thyrotropin secretion in euthyroid subjects. *J Clin Endocrinol Metab* 51:399–403, 1980
10. Cronk CE, Roche AF: Rare- and sex-specifc reference data for triceps and subscapular skinfolds and weight/stature. *Am J Clin Nutr* 35:347–354, 1982
11. Sargent JA, Gotch FA: The analysis of concentration dependence of uremic lesions in clinical studies. *Kidney Int* 7:S35–S44, 1975
12. Sargent J, Gotch F, Borah M, Piercy L, Spinozzi N, Schoenfeld P, Humphreys M: Urea kinetics: a guide to nutritional management of renal failure. *Am J Clin Nutr* 31:1696–1702, 1978
13. Zavala DC, Printen KJ: Basal and exercise tests on morbidly obese patients, pre and post gastric bypass. *Surgery* 95:221–229, 1984
14. Fomon SJ, Thomas LN, Jensen RL, May CD: Determination of nitrogen balance of infants less than 6 months of age. *Pediatrics* 22:94–100, 1958
15. Nicoloff JT, Low JC, Dussault JH, Fisher DA: Simultaneous measurement of thyroxine and triiodothyronine peripheral turnover kinetics in man. *J Clin Invest* 51:473–483, 1972
16. Surks MI, Schadlow AR, Stock JM, Oppenheimer JH: Determination of iodothyronine absorption and conversion of L-thyroxine (T_4) to L-triiodothyronine (T_3) using turnover rate techniques. *J Clin Invest* 52:805–811, 1973
17. Carter WJ, Shakir KM, Hodges S, Faas FH, Wynn JO: Effect of thyroid hormone on metabolic adaptation to fasting. *Metabolism* 24:1177–1183, 1975
18. Carter WJ, Faas FH, Wynn JO: Role of starvation in production of creatinuria in experimental hyperthyroidism. *Metabolism* 26:1243–1250, 1977
19. Burman KD, Wartofsky L, Dinterman RE, Kesler P, Wannemacher RW Jr: The effect of T_3 and reverse T_3 administration on muscle protein catabolism during fasting as measured by 3-methylhistidine excretion. *Metbolism* 28:805–813, 1979
20. Haverberg LN, Deckelbaum L, Bilmazes C, Munro HN, Young VR: Myofibrillar protein turnover and urinary 3-methylhistidine output. *Biochem J* 152:503–510, 1975
21. Mitch WE: Amino acid release from the hindquarter and urea appearance in acute uremia. *Am J Physiol* 241 (*Endocrinol Metab* 4):E415–E419, 1981
22. Clark AS, Mitch WE: Muscle protein turnover and glucose uptake in acutely uremic rats. *J Clin Invest* 72:836–845, 1983
23. Holliday MA, Chantler C, MacDonnell R, Keitges J: Effect of uremia on nutritionally-induced variations in protein metabolism. *Kidney Int* 11:236–245, 1977
24. Garber AJ: Skeletal muscle protein and amino acid metabolism in experimental chronic uremia in the rat. Accelerated alanine and glutamine formation and release. *J Clin Invest* 62:623–632, 1978
25. Li JB, Wassner SJ: Muscle degradation in uremia: 3-methylhistidine release in fed and fasted rats. *Kidney Int* 20:321–325, 1981
26. Ganda OP, Aoki TT, Soeldner JS, Morrison RS, Cahill GH: Hormone-fuel concentrations in anephric subjects. Effect of

hemodialysis (with special reference to amino acids). *J Clin Invest* 57:1403–1411, 1976

27. BORAH MF, SCHOENFELD PY, GOTCH FA, SARGENT JA, WOLFSON M, HUMPHRIES MH: Nitrogen balance during intermittent dialysis therapy of uremia. *Kidney Int* 14:491–500, 1978
28. KOPPLE JD: Dietary requirements, in *Clinical aspects of uremia and dialysis,* edited by MASSRY SG, SELLERS AL, Springfield, Charles C Thomas, 1976, p 467
29. GARDNER DF, KAPLAN MM, STANLEY CA, UTIGER RD: Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. *N Engl J Med* 300:579–584, 1979
30. WIMPFHEIMER C, SAVILLE E, VOIROL MJ, DANFORTH E JR, BURGER AG: Starvation-induced decreased sensitivity of resting metabolic rate to triiodothyronine. *Science* 205:1272–1273, 1979